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(54) Title: MULTILAYER CONTROLLED RELEASE TABLETS CONTAINING BOTH NAPROXEN AND NAPROXEN SODIUM SALT

(57) Abstract

The present invention relates to controlled release dosage forms composed of a naproxen layer which contains a delayed release granulate of naproxen compressed with an immediate release granulate of naproxen and an immediate release naproxen sodium layer compressed with the naproxen layer, designed to promptly exert a therapeutic effect while also maintaining the therapeutic blood concentration for a prolonged duration of 24 hours.

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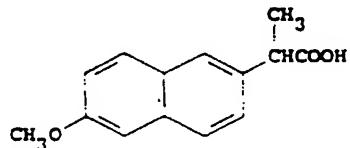
MULTILAYER CONTROLLED RELEASE TABLETS CONTAINING BOTH NAPROXEN AND NAPROXEN SODIUM SALT

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The invention herein is directed to new controlled release multi-layer pharmaceutical compositions containing a combination of naproxen and naproxen sodium. The first layer of the pharmaceutical composition consists of delayed release granulates of naproxen compressed together with immediate release granulates of naproxen. A layer of immediate release naproxen sodium is compressed onto the first layer of naproxen forming an adjacent layer or layers.

25

Naproxen, [(S)-6-methoxy- α -methyl-2-naphthaleneacetic acid, hereinafter also referred to as naproxen acid] is of the formula



30

Naproxen is widely used (in such an acid state) as an anti-inflammatory compound in the treatment of arthritis, and as an analgesic and antipyretic in the treatment of mild to moderate pain, such as dysmenorrhea or arthritis.

35

Naproxen has a low water solubility and a comparatively slow rate of absorption which is a disadvantage when using naproxen as an analgesic. This

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drawback is overcome by the use of its salt, naproxen sodium. Naproxen sodium is the sodium salt of naproxen acid. Naproxen sodium, due to its higher water solubility, has a comparatively faster rate of absorption leading to a prompt analgesic and antipyretic effect. Hence, naproxen sodium is the drug of choice in the treatment of mild to moderate pain where a prompt therapeutic effect is desired. After absorption, both naproxen and naproxen sodium exist in the circulating blood as naproxen anions.

Naproxen is available in 250 mg, 375 mg and 500 mg tablets and is generally administered in therapeutic doses of 500-1000 mg per day, while naproxen sodium is available in 275 mg and 550 mg tablets and is administered in therapeutic doses of 550-1100 mg per day. Both compounds have multiple frequencies of administration of 8-12 hours every day.

Conventional dosage forms of naproxen or naproxen sodium are administered two to three times daily to maintain therapeutic blood levels which results in a large fluctuation in peak and trough blood levels. Controlled release dosage forms for naproxen have been designed to overcome this drawback by reducing the fluctuation and maintaining the desired therapeutic blood concentration as well as reducing the frequency of drug administration.

Hsias and Kent (U.S. Patent Nos. 4,571,333 and 4,803,079) disclose the use of controlled release

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naproxen formulations and disclose the use of controlled release naproxen sodium formulations.

Therapeutic blood peak levels of naproxen are not achieved promptly by these formulations and take greater than 6 hours to be achieved, as indicated by the maximum concentrations (C_{max}) disclosed therein.

5 Rotini and Marchi (U.S. 4,888,178) disclose galenic formulations made of a mixture of immediate release naproxen granulate and a controlled release 10 naproxen granulate. Naproxen, in its acid form (naproxen acid), is used in both the immediate release granulate and the controlled release granulate.

Although the concept of using either naproxen or naproxen sodium independently in controlled release 15 dosage forms has been demonstrated, the art available has several disadvantages. First, the relevant art demonstrates that therapeutic blood levels, as indicated by the maximum concentration (C_{max}) are not achieved promptly to exert a fast therapeutic response.

20 Such a delay in reaching therapeutic blood levels is unsuitable for use as an analgesic and antipyretic in the treatment of mild to moderate pain such as dysmenorrhea or arthritis, where fast onset of action is necessary to obtain pain relief.

25 Furthermore, utilizing naproxen sodium alone in a controlled release system disclosed in the relevant art results in failure to maintain therapeutic blood concentration for a prolonged duration of 24 hours

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since its higher solubility will not delay the release of the compound from the dosage form at a rate comparable to naproxen.

In addition, matrix systems described in the art
5 are designed to remain intact, and since naproxen and naproxen sodium are known to be irritants to the gastrointestinal tract, such systems may not empty from the stomach due to its large size. The retention of such systems in the stomach may thereby cause gastric
10 damage.

It would be desirable to provide a pharmaceutical composition that achieves a therapeutic blood level of naproxen anions promptly to exert a fast therapeutic analgesic effect, which composition also maintains the
15 therapeutic blood concentration for a prolonged duration of 24 hours being therefore suitable for once a day administration and which does not remain intact as a matrix.

Summary of the Invention

20 The present invention relates to controlled release preparations containing a combination of naproxen sodium and naproxen acid. Specifically, it relates to a multilayer oral dosage form comprising a layer of naproxen comprised of a delayed release
25 granulate of naproxen compressed with an immediate release granulate of naproxen. The delayed release naproxen is a mixture of naproxen with retarding agents, hydrogenated castor oil and ethylcellulose.

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The immediate release naproxen is a granulate of naproxen.

The compressed delayed release naproxen and immediate release naproxen (hereinafter the naproxen 5 layer) are then compressed with a layer of immediate release naproxen sodium granulate (hereinafter the naproxen sodium layer). The tablet is designed to provide prompt therapeutic plasma levels of naproxen in less than 1 hour and maintain these levels for a 10 duration of 24 hours, thereby providing for once daily administration. The tablet is designed to disintegrate, rather than remain as a matrix in the stomach, thereby reducing the potential for gastric irritation and variability in absorption.

15 The invention herein will be more fully understood with regard to the following brief description of the accompanying drawings and the following detailed description of the invention.

Brief Description of the Drawings

20 Figure 1 is a cross sectional representation of a tablet of the pharmaceutical composition described herein.

Figure 2 is a cross sectional representation of a second embodiment of a tablet of the pharmaceutical 25 composition described herein.

Figure 3 is a cross sectional representation of a third embodiment of a tablet of the pharmaceutical composition described herein.

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Figure 4 is a graphical representation of the plasma profiles of two different naproxen and naproxen sodium controlled release formulations, of an immediate release naproxen sodium formulation and of a controlled release naproxen acid formulation, over 24 hours.

Figure 5 is a graphical representation of the plasma profiles of two different naproxen and naproxen sodium controlled formulations, of an immediate release naproxen sodium formulation and of a controlled release naproxen acid formulation, over the initial four hours following administration.

Detailed Description of the Invention

The present invention is directed to multilayer controlled release preparations containing a layer of compressed delayed and immediate release granulates of naproxen and a layer of naproxen sodium. Such a dosage form, immediately releasing naproxen sodium, provides a fast rate of absorption, achieving a desired therapeutic plasma level in less than 1 hour. The subsequent disintegration and release of the immediate and delayed release granulates of naproxen maintains the therapeutic blood levels for a duration of 24 hours, thereby providing once daily administration. The compositions achieve a therapeutic effect which is prompt and maintained for a longer duration while disintegration of the tablet reduces gastric retention time thereby reducing the potential for gastric irritation and damage. The compositions reduce

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variability of absorption of naproxen thereby leading to predictable bioavailability.

As used herein the terms "multilayer" or "multilayered" encompass tablets consisting of two or 5 more adjacent layers, including but not limited to, bilayer and trilayer tablets and compositions consisting of a coating surrounding an inner core. Types of multilayer pharmaceutical compositions and methods of manufacturing such compositions are well 10 known in the pharmaceutical art. The terms "core" or "coating" are used herein synonymously with the term "layer" which is further described in the detailed description of the drawings herein.

The precise amounts of naproxen sodium and 15 naproxen needed to achieve therapeutic blood concentration are calculated by means of pharmacokinetic modelling and pharmacodynamic response. (See Thomson et al., Clin. Pharmacol. Ther., Feb. 1981, 29(2) p.168-73 for plasma concentration profiles.)

20 More specifically, the present invention is a controlled release pharmaceutical composition containing naproxen sodium present in an amount from about 5 to about 30 w/w% of the compositions of the present invention, more preferably from about 10 to 25 about 25 w/w% and most preferably from about 10 to about 15 w/w%.

Preferably, the percent of naproxen acid present in the pharmaceutical composition of the present

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invention is from about 35 to about 75 w/w% of the compositions of the present invention, more preferably from about 45-65 w/w% and most preferably from about 50-60 w/w%.

5 Preferably, the total composition is formed from a mixture of:

54.3% w/w naproxen;

14.4% w/w naproxen sodium;

1.8% w/w lactose;

10 18.3% w/w hydrogenated castor oil;

5.8% w/w ethyl cellulose;

3.6% w/w polyvinylpyrrolidone; and

1.8% w/w other pharmaceutically acceptable excipients and lubricating agents.

15 The pharmaceutical compositions of the present invention can be described with regard to the accompanying drawings, Figures 1, 2 and 3 schematically representing embodiments of the invention, the preferred embodiment being represented by the tablet of
20 Figure 1.

Figure 1 represents a cross sectional view of a pharmaceutical composition herein. The pharmaceutical composition consists of a bilayer tablet (18) which can have any geometric shape, although for ease of
25 description herein, an oval cross section is shown. The tablet (18) includes a naproxen layer (20) which includes, as the pharmaceutically active component, naproxen acid and other pharmaceutically acceptable

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excipients. The naproxen acid in the naproxen layer consists of an immediate release naproxen granulate (23) and a delayed release naproxen granulate (24). The naproxen layer (20) can be formulated by

5 compression of the naproxen acid granulates with any suitable tabletting equipment. Standard compression tabletting techniques can be employed for forming the naproxen layer. The naproxen layer of the present invention can be prepared according to the methodology

10 of Rotini and Marchi, U.S. 4,888,178, hereby incorporated by reference. The ratio of the immediate release naproxen granulate to the delayed release naproxen granulate can be as described in the 4,888,178 patent.

15 Adjacent to the naproxen layer (20) is a naproxen sodium layer (22) consisting of naproxen sodium and other pharmaceutically acceptable excipients. The naproxen sodium layer can be applied to the naproxen layer by compression or spraying techniques, such as

20 are well known in the tabletting art. The naproxen sodium in the naproxen sodium layer can be present in any therapeutically acceptable amount.

Figure 2 represents an cross sectional view of an second embodiment of a pharmaceutical composition

25 herein. The pharmaceutical composition consists of a trilayer tablet (26) which can have any geometric shape, although for ease of description herein, an oval cross section is shown. The tablet (26) includes a

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naproxen layer (30) which includes, as the pharmaceutically active component, naproxen acid and other pharmaceutically acceptable excipients. The naproxen acid in the layer consists of an immediate release naproxen granulate (31) and a delayed release naproxen granulate (32) as described above. The naproxen layer (30) can be formulated by compression of the naproxen acid granulates with any suitable tabletting equipment. Standard compression tabletting techniques can be employed for forming the naproxen layer.

Adjacent to the naproxen layer (30) are two layers (28) consisting of naproxen sodium and other pharmaceutically acceptable excipients. The naproxen sodium layers (28) can be applied by compression and spraying techniques, such as are well known in the tabletting art. The naproxen sodium in the layer can be present in any therapeutically acceptable amount.

Figure 3 represents a cross sectional view of a third embodiment of a pharmaceutical composition herein. The pharmaceutical composition consists of a tablet (10) which can have any geometric shape, although for ease of description herein an oval cross section is shown. The tablet (10) includes an inner core (12) which includes, as the pharmaceutically active component, naproxen acid and other pharmaceutically acceptable excipients. The naproxen acid in the core consists of an immediate release

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naproxen granulate (13) and a delayed release naproxen granulate (14) as described above. The core (12) can be formulated by compression of the naproxen acid granulates with any suitable tabletting equipment.

5 Standard compression tabletting techniques can be employed for forming the core.

Surrounding the core is a coating (16) consisting of naproxen sodium and other pharmaceutically acceptable excipients. The coating can be applied by 10 coating techniques, such as are well known in the tabletting art. The naproxen sodium in the coating can be present in any therapeutically acceptable amount.

The naproxen acid in the naproxen layer can be present in any therapeutically acceptable amount.

15 Naproxen is present in the naproxen layer in immediate and delayed release granulates in amounts effective for maintaining therapeutic blood levels of naproxen anions over a period of 24 hours. Naproxen administered independently is generally administered in therapeutic 20 doses of about 500 to 1000 mg per day. The naproxen present in the naproxen layer of the pharmaceutical compositions herein can therefore be present in an amount to accomplish such dosing regimen in combination with the naproxen sodium of the immediate release 25 layer. For the practice of the invention herein the amount of naproxen acid in the naproxen layer is generally present in an amount from about 35 to about 75 w/w% of the composition, and preferably from about

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45 to about 65 w/w% and more preferably from about 50 to about 60 w/w%. Various pharmaceutically acceptable excipients can be combined with the naproxen acid granulates, as is well known in the pharmaceutical art.

5 The naproxen sodium in the naproxen sodium layer can be present in any therapeutically acceptable amount. Naproxen sodium administered independently is generally administered in therapeutic doses of 550-1100 mg per day. The naproxen sodium layer of the
10 pharmaceutical composition herein is preferably in an amount to accomplish such dosing regimen in combination with the naproxen acid of the naproxen layer. The amount of naproxen sodium in the naproxen sodium layer is generally in an amount from about 5 to about 30 w/w%
15 of the compositions of the present invention, preferably from about 10 to about 25 w/w% and more preferably from about 10 to about 15 w/w%. Various pharmaceutically acceptable excipients can be combined with the naproxen sodium in the naproxen sodium layer
20 as is well known in the pharmaceutical art.

In the preparation of the formulations of the present invention, an immediate release naproxen granulate is prepared by dry granulating the active agent naproxen with suitable adjuvant agents like
25 binding, disintegrating and lubricating agents and then sifting the granules on a sieve having meshes of 1 mm.

Exemplary of such binding agents are polyvinylpyrrolidone, carboxymethylcellulose,

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microcrystalline cellulose, lactose, saccharose, mannitol, gumarabic, pectin, gelatin and the like.

Representative disintegrating agents include starch, sodium starch glycolate, alginates, 5 polyvinylpyrrolidone and the like.

Examples of lubricating agents are talc, magnesium stearate, stearic acid, silica gel and the like.

A delayed release naproxen granulate is prepared by wet granulating the active agent with retarding 10 agents by means of a solvent selected from an alcohol containing from 1 to 4 carbon atoms, an aromatic hydrocarbon, a ketone containing from 3 to 6 carbon atoms, an alkyl halide containing from 1 to 4 carbon atoms, mixtures thereof or mixtures thereof with water, 15 then drying the granules in an oven at 50°C and sifting them through a sieve having meshes of 1 mm. The preferred solvent being 95% ethyl alcohol.

Representative retarding agents are ethylcellulose, methylcellulose, polyvinylacetate, 20 methacrylic acid esters, cellulose acetate, fatty alcohols containing from 12 to 32 carbon atoms, glyceric esters of fatty acids containing from 10 to 22 carbon atoms, like the mono- and di-stearate of glycerol, esters of fatty acids and alcohols having 25 from 12 to 31 carbon atoms, paraffin, natural waxy substances like beeswax, unbleached wax, candelilla wax, carnauba wax, sealing wax, spermaceti, ozokerite and hydrogenated vegetable oils like hydrogenated

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castor oil, hydrogenated peanut oil, hydrogenated cotton seed oil and mixtures thereof.

Methylcellulose, ethylcellulose, hydrogenated vegetable oils and mixtures thereof are preferred 5 retarding agents in the present invention.

The immediate release naproxen granulate and the delayed release naproxen granulate are mixed and compressed in such weight ratios that the active principle contained in the final naproxen layer is in 10 the amounts described supra.

The immediate release naproxen sodium layer granulate is prepared by solubilizing polyvinylpyrrolidone in ethyl alcohol, adding a dye, mixing in the naproxen sodium, drying the granules in 15 an oven and sifting them through a sieve having meshes of 1 mm.

The naproxen sodium layer particles are mixed with additional pharmaceutically acceptable excipients and compressed or sprayed onto the naproxen layer to form a 20 naproxen sodium layer partially or entirely surrounding the naproxen layer, according to conventional methods well known in the tabletting art.

The following examples 1-3 illustrate the methods used to prepare the compositions of the invention. 25 These examples are given by way of illustration only and are not to be construed as limiting the invention in spirit or scope, as many modifications in materials

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and methods will be apparent from this disclosure to
one having ordinary skill in the art.

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Example 1

A pharmaceutical composition consisting of an immediate and delayed release naproxen acid granulate layer and an immediate release naproxen sodium layer
5 was prepared according to the following methodology.

(This methodology results in a 2,000 tablet yield.)

A) Naproxen sodium granulate (for the naproxen sodium layer)

	Naproxen sodium	300 g.
10	PVP K30	12
	Dye (yellow) E 102	2
	Ethyl alcohol	45

PVP K30 was solubilized in 45 grams of ethyl alcohol, the dye was added and mixed with the naproxen sodium for 5 minutes in a mixer. The mixture was granulated by extrusion and dried in an oven at 35°C. The dried product was sifted on a 1 mm size sieve.

B) Naproxen acid granulate (immediate release)

	Naproxen acid	130 g.
20	Starch	13
	Lactose	38.48
	Sodium starch glycolate	7.8
	PVP K90	7.8
	Magnesium stearate	0.52
25	95% ethyl alcohol	3.458

The powders were mixed for 15 minutes in a granulator. Ethyl alcohol was sprayed onto the powder mixture and mixing was continued for 10 minutes. The

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dried granulation was then passed through a 1.25 mm sieve.

C) Naproxen acid granulate (delayed release)

	Naproxen acid	1000 g.
5	Ethyl-cellulose	120
	Hydrogenated castor oil	380
	Ethyl alcohol	402.24

The powders were mixed for 60 minutes in a mixer and then mixed with ethyl alcohol for 10 minutes.

10 Granulation was done by extrusion and was dried at 50°C. The dried product was sifted using a 1 mm sieve.

D) Formation of the naproxen layer

15 The immediate release and delayed release granulates of naproxen acid were mixed with PVP CL micronized (68 g.) for 10 minutes. The granulation mixture was compressed with a suitable punch to form a layer of naproxen acid.

E) Compression of the naproxen layer with the naproxen sodium layer

20 The naproxen layer was compressed with naproxen sodium granulate using a suitable punch to form a bi-layered tablet having separate layers of naproxen and naproxen sodium.

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Example 2

A pharmaceutical composition was prepared consisting of an immediate and delayed release naproxen acid granulate layer and an immediate release naproxen sodium layer according to the method of Example 1. The tablet had the following composition:

NAPROXEN SODIUM LAYER

10	Naproxen Sodium	mg	150
	PVP K 30	mg	6
	Yellow Dye E 102	mg	1

NAPROXEN LAYER

15	Cornstarch	mg	8.16
	Lactose	mg	24.18
	Sodium starch glycolate	mg	4.92
	PVP K 90	mg	4.92
	Magnesium stearate	mg	0.33
	Hydrogenated castor oil	mg	140.22
20	Ethyl cellulose	mg	44.28
	PVP C.L.	mg	20.4
	Naproxen Acid	mg	<u>450</u>
	Total Weight	mg	854.41

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Example 3

A pharmaceutical composition was prepared consisting of an immediate and delayed release naproxen acid granulate layer and an immediate release naproxen sodium layer according to the method of example 1. The tablet had the following composition:

NAPROXEN SODIUM LAYER

10	Naproxen Sodium	mg	150
	PVP K 30	mg	6
	Yellow Dye E 102	mg	1

NAPROXEN LAYER

15	Cornstarch	mg	6.5
	Lactose	mg	19.24
15	Sodium glycolate starch	mg	3.9
	PVP K 90	mg	3.9
	Magnesium stearate	mg	0.26
	Hydrogenated castor oil	mg	190
	Ethylcellulose	mg	60
20	PVP C.L.	mg	34
	Naproxen Acid	mg	<u>565</u>
	Total Weight	mg	1039.80

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Pharmacokinetic tests have been carried out in man to verify the onset and duration of naproxen plasma levels for the above described formulations. These pharmacokinetic tests have been performed on groups 5 each consisting of six healthy volunteers, by examining the hematic levels of naproxen at various time points from 0.3 up to 72 hours after the administration of the compositions.

The values reported in the following Tables I and 10 II are calculated from the mean of the values of the single values of the six healthy volunteers. The naproxen was checked in the plasma by spectrophotometric methodology at 272 nm after passing through a high pressure liquid chromatography column 15 (HPLC); the values are expressed in mcg/ml of plasma.

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TABLE I
Hematic Levels of Naproxen
Formulation of Example 3

5

	<u>Time (hrs)</u>	<u>Hematic Levels of Naproxen</u> (mean value mcg/ml)
10	0.3	34.2
	0.6	41.7
	1	50.2
	2	57.4
	3	63.0
15	4	61.1
	6	56.1
	8	50.8
	12	45.3
	24	33.0
20	48	13.5
	72	5.7

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TABLE II

Hematic Levels of Naproxen

Formulation of Example 2

5

	<u>Time (hrs)</u>	<u>Hematic Levels of Naproxen</u> (mean value mcg/ml)
10	0.5	37.0
	1	49.8
	2	57.1
	3	59.7
15	4	59.4
	6	50.6
	8	44.5
	12	35.7
	24	21.6
20	48	7.7
	72	3.2

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Figure 4 is a graphical representation of the plasma profile of two formulations of controlled release naproxen and naproxen sodium, of an immediate release formulation of naproxen sodium and a controlled release naproxen formulation, over 24 hours. Figure 5 is an enlargement of the plasma profiles for the same four formulations for the initial four hours, after administration.

10 It is shown in Figures 4 and 5 that the compositions of the present invention, Examples 2 and 3 reach therapeutic blood plasma levels in less than one hour. Figure 4 shows that the compositions of Examples 2 and 3 maintain therapeutic blood levels over a period 15 of 24 hours.

Figure 4 shows that Anaprox®, (described in the Physician's Desk Reference, 46th edition 1992, as an immediate release naproxen sodium tablet, commercially available from Syntex) achieves therapeutic blood 20 levels within 0.5 hours but as shown in Figure 4, the therapeutic blood levels are not maintained over a period of 24 hours and thus that composition would not be useful for once daily administration. Xenar, CR (a controlled release naproxen acid tablet, commercially 25 available in Italy from Alfa Pharmaceuticals) as is shown in Figure 5, does not achieve therapeutic blood levels for almost two hours and thus would not be useful for immediate relief from pain.

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A particularly beneficial aspect of the invention herein, as shown in the graphs, is that the immediate release naproxen sodium layer allows for faster absorption thereby providing for pain relief within an 5 hour. Figure 4 shows the added benefit that the controlled release layer of naproxen acid maintains the therapeutic blood levels for a duration of 24 hours thereby providing for once daily administration. Additionally, the design of the tablet provides for 10 total disintegration of the tablet thereby reducing the potential for gastric irritation and damage.

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What is claimed is:

1. A controlled release pharmaceutical composition comprising:
 - 5 a layer of naproxen; and
 - a layer of naproxen sodium.
2. A controlled release pharmaceutical composition according to Claim 1 wherein the naproxen layer
10 comprises:
 - an immediate release granulate of naproxen;
 - and
 - a delayed release granulate of naproxen.
- 15 3. A controlled release pharmaceutical composition according to Claim 2 wherein the naproxen sodium is present in an amount from about 5-30 w/w% of the composition.
- 20 4. A controlled release pharmaceutical composition according to Claim 3 wherein the naproxen is present in an amount from about 35-75 w/w% of the composition.
- 25 5. A controlled release pharmaceutical composition according to Claim 4 wherein the naproxen sodium is present in an amount from about 10-25 w/w% of the composition.

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6. A controlled release pharmaceutical composition according to Claim 5 wherein the naproxen is present in an amount from about 45-65 w/w% of the composition.

5

7. A controlled release pharmaceutical composition according to Claim 6 wherein the naproxen sodium is present in an amount from about 10-15 w/w% of the composition.

10

8. A controlled release pharmaceutical composition according to Claim 7 wherein the naproxen is present in an amount from about 50-60 w/w% of the composition.

15

9. A method of treating mild to moderate pain comprising administering a controlled release pharmaceutical composition comprising:
 - a layer of naproxen; and
 - a layer of naproxen sodium.

20

10. A method according to Claim 9 wherein the naproxen layer comprises:

25

- an immediate release granulate of naproxen;
 - and
 - a delayed release granulate of naproxen.

11. A method according to Claim 10 wherein the pain is associated with dysmenorrhea.

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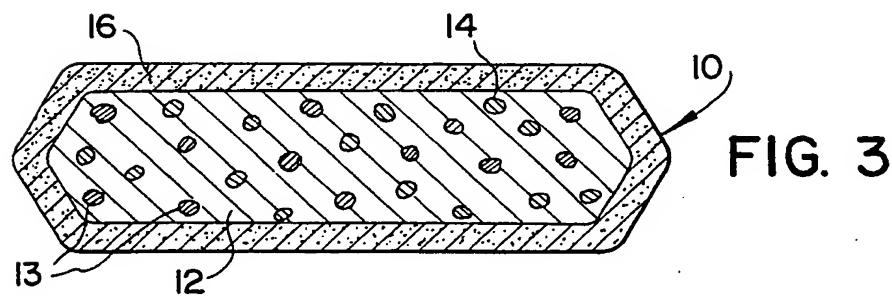
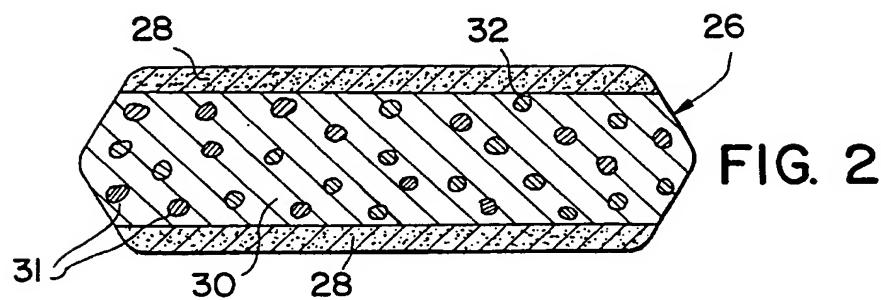
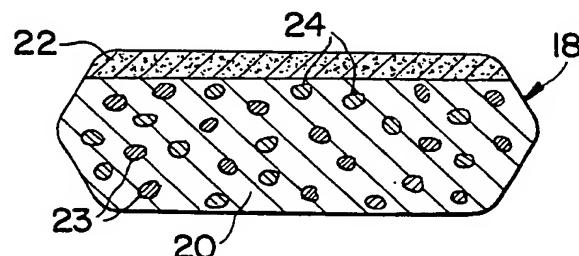
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**12. A method according to claim 10 wherein the pain is
associated with arthritis.**

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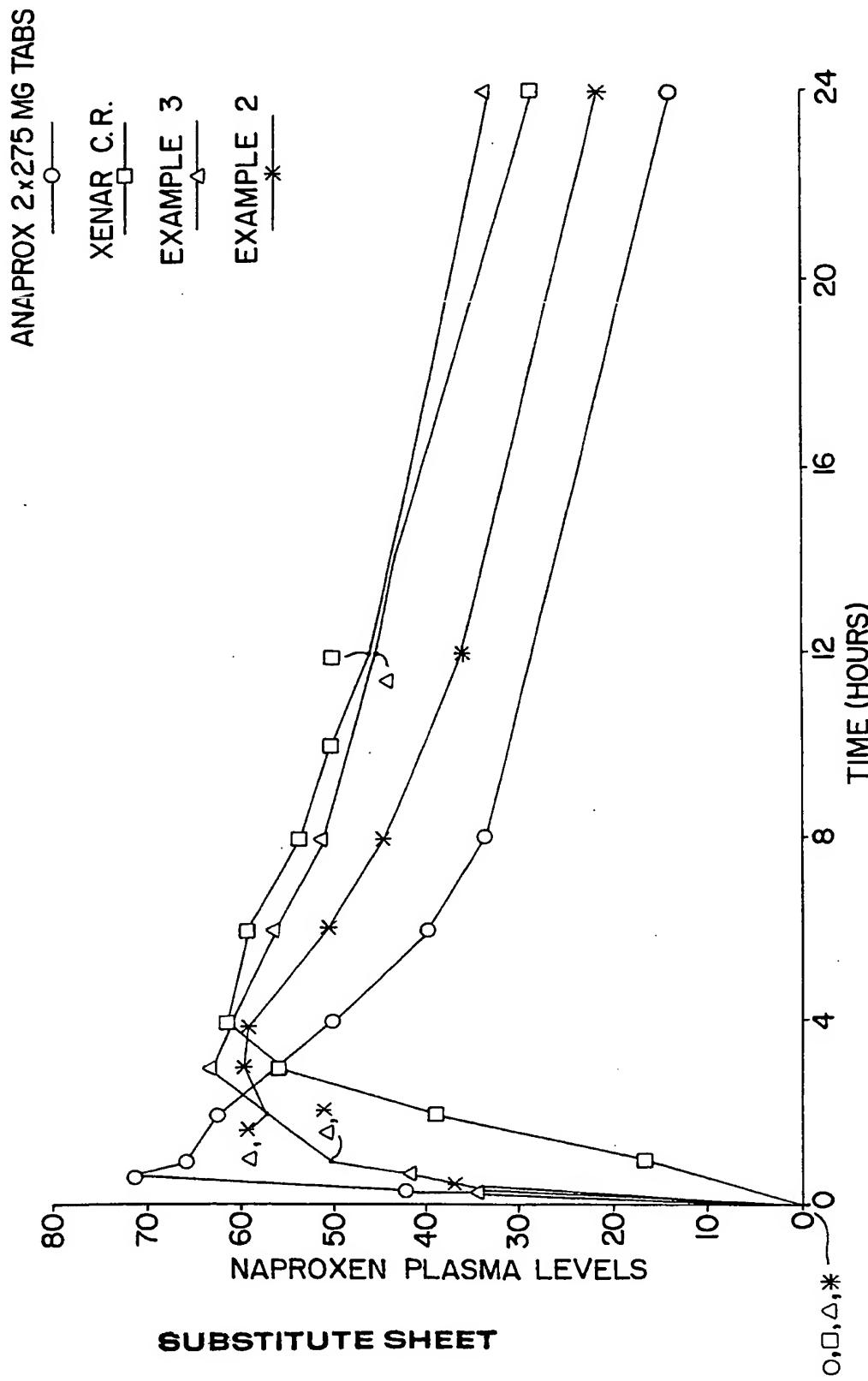
SUBSTITUTE SHEET

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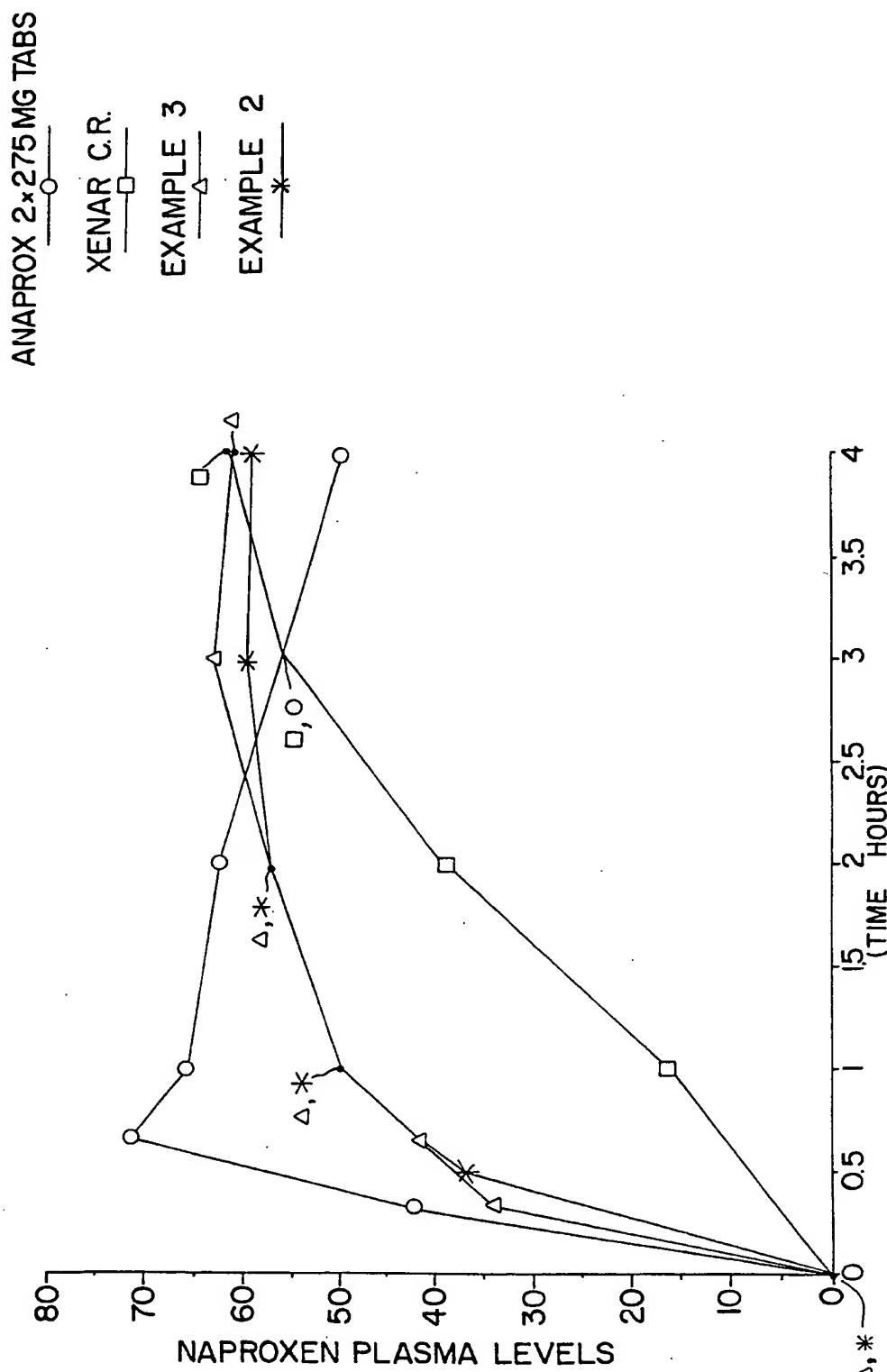
FIG. 4
**COMPARATIVE PLASMA PROFILE OF ANAPROX 2x275 MG,
 XENAR C.R. 750MG, AND DYSPROX C.R.600 AND 700 MG**



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FIG. 5**COMPARATIVE PLASMA PROFILE OF ANAPROX 2x275 MG,
XENAR C.R. 750MG, AND DYSPROX CR. 600 AND 700MG****SUBSTITUTE SHEET**

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 92/09129

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC Int.C1. 5 A61K31/19; A61K9/20		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.C1. 5	A61K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	EP,A,0 274 734 (PHARMAIDEA) 20 July 1988 see claims see example 4 ---	1-12
A	EP,A,0 438 249 (ELAN) 24 July 1991 see claims see examples ---	1-12
A	EP,A,0 324 981 (ALFA WASSERMAN) 26 July 1989 see claims see example 1 -----	1-12
* Special categories of cited documents : ¹⁰ "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed		"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family
IV. CERTIFICATION		
Date of the Actual Completion of the International Search 27 APRIL 1993	Date of Mailing of this International Search Report <i>26.93</i>	
International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer SCARPONI U.	

INTERNATIONAL SEARCH REPORT

1. national application No.
PCT/ US 92/ 09129

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
ALTHOUGH CLAIMS 9-12 ARE DIRECTED TO A METHOD OF TREATMENT OF THE HUMAN BODY BY THERAPY(RULE 39.1(IV)PCT) THE SEARCH HAS BEEN CARRIED OUT AND BASED ON THE ALLEGED EFFECTS OF THE COMPOSITION.
2. Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

US 9209129
SA 66417

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 27/04/93

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0274734	20-07-88	AU-B-	610112	16-05-91
		JP-A-	63190822	08-08-88
		US-A-	4865849	12-09-89
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EP-A-0438249	24-07-91	AU-A-	6933291	18-07-91
		JP-A-	4217918	07-08-92
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EP-A-0324981	26-07-89	AU-A-	2766689	20-07-89
		JP-A-	1279823	10-11-89
		US-A-	5043167	27-08-91
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